

able to citizens of low income groups, and that, without governmental intervention, control and regimentation.

Certainly, such a happy consummation should appeal to every member of the California Medical Association, and all should work for so laudable an objective.

#### NEXT YEAR'S ANNUAL SESSION

**The Meeting Dates for 1945 Are May 6-7.**—In May last, the House of Delegates approved the recommendation of the Council that next year's Annual Session shall be held on Sunday-Monday, May 6-7, 1945, in Los Angeles. That will mark the third successive year in which the Los Angeles County Medical Association will have been the nominal host of the California Medical Association.

Reasons for the selection are simple: the Association has thirteen Scientific Sections, a House of Delegates, a Council, and a Woman's Auxiliary; and for each of these separate activities, a meeting room is needed. The Hotel Del Monte, where the C.M.A. has met year after year, is now a Navy institution; San Francisco, at present a major port of embarkation, finds its hotels constantly filled to overflowing; consequently, the Hotel Biltmore in Los Angeles, with its battery of conference rooms, is the only hostelry in which even approximate meeting needs can be provided. Therefore, during the Duration, it may be assumed that we will continue to meet in Los Angeles, provided the Hotel Biltmore is available.

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**Advice to Prospective Essayists.**—The above comments having been made, it is now in order to remind members of the California Medical Association who are in position to cooperate, to write to the proper Section Secretary (or to the Association Secretary, who is chairman of the Committee on Scientific Work) concerning possible papers to be presented at Section or General Meetings. Members who are interested in special topics are also invited to send in suggestions. The C.M.A. Committee and Section Officers will be happy to receive such. No scientific exhibits are contemplated. Following the procedure in operation during the last two Annual Sessions, next year's—the C.M.A.'s Seventy-fourth—will be limited to two-day, streamlined meetings. The two days thus designated,—Sunday and Monday,—make for greater ease in attendance, since appointments and other professional work can be better set aside at that period of the week.

Members should keep the next Annual Session in mind, and if possible, make plans to be present. During these strenuous days, the interchange of opinion on old and new problems is as much needed as ever. With the large membership in the Los Angeles County Medical Association, in excess of two thousand, there exists a substantial nucleus for a successful session. Make plans to be among those who will be present.

## EDITORIAL COMMENT†

### POTENTIATED INFLUENZA VACCINE

Ten years ago Burky<sup>1</sup> found that while autogenous lens and muscle proteins are apparently nonantigenic for rabbits, both become effective antigens when combined with staphylococcus filtrate. Using the combined antigens rabbits can be readily sensitized to their own crystalline lens and skeletal muscles. Such rabbits produce sufficiently high titer anti-lens or anti-muscle precipitins to cause degenerative lesions in its own homologous tissues.

Since publication of these results the suggested possibility of enhancing the immunizing power of numerous relatively unsuccessful vaccines by the addition of adjuvants has been the subject of numerous investigations. Ramon<sup>2</sup> found that the addition of lanolin to diphtheria toxin enhances antitoxin production. Freund<sup>3</sup> noted that the addition of paraffin oil enhances the antigenic properties of heat-killed tubercle bacilli. Landsteiner<sup>4</sup> was able to sensitize animals to certain relatively simple chemical compounds by means of simultaneous intraperitoneal injection of these compounds and heat-killed tubercle bacilli suspended in paraffin oil.

Combining these suggestive leads Freund<sup>5</sup> of the Department of Health, New York City, attempted to maximize the antigenicity of horse serum. The horse serum was added to an equal volume of "aquaphor," a lanolin-like substance which possesses a much greater water-absorbing capacity than lanolin. There was then added to the mixture an equal volume of paraffin oil containing 2 mg. per c.c. of vacuum dried, heat-killed tubercle bacilli. The resulting emulsion was injected in 0.5 c.c. doses intramuscularly into full-grown guinea pigs. Each dose contained 0.125 c.c. horse serum, 0.125 c.c. of the lanolin-like substance, 0.25 c.c. paraffin oil and 0.5 mg. heat-killed tubercle bacilli. Control animals were injected with the same dose of horse serum diluted with saline solution.

The animals were tested for sensitivity by intracutaneous injections of graded dilutions of horse serum at various intervals during the next 12 months. Necrosis occurred frequently at the site of the injection of 10 per cent horse serum in groups sensitized with horse serum plus adjuvants, but was never noted in control groups sensitized with horse serum alone. The contrast was particularly striking in animals tested one year after sensitization. Tested with 1:10 dilution of horse serum a typical late reaction in the adjuvant groups was an area of redness 35 mm. in diameter, with a 3 mm. swelling. The reactions were wholly negative in the control groups.

† This department of CALIFORNIA AND WESTERN MEDICINE presents editorial comments by contributing members on items of medical progress, science and practice, and on topics from recent medical books or journals. An invitation is extended to all members of the California Medical Association to submit brief editorial discussions suitable for publication in this department. No presentation should be over five hundred words in length.

Four weeks after the antigenic injection the serums of the control groups gave an average + precipitin reaction when tested with a 1:10 dilution of horse serum, but negative precipitin reactions when tested with a 1:100 serum dilution. The groups sensitized with horse serum plus adjuvants gave +++ precipitin reactions with 1:10 serum dilution, and + reactions with dilutions as high as 1:1000. This suggested that the addition of the immunologic adjuvants increases the immunizing power of horse proteins at least 100-fold.

A most promising practical application of the Freund technique is currently reported by Friedewald<sup>6</sup> of the International Health Division, Rockefeller Foundation. He blended allantoic fluid suspensions of formalin-killed influenza virus with a half volume of the lanolin-like substance "falba." To this was added an equal volume of paraffin oil containing heat-killed virulent tubercle bacilli. Each c.c. of the resulting emulsion contained 1.5 mg. of the vacuum dried tubercle bacilli. He tested the immunizing capacity of a single 0.5 c.c. subcutaneous injection of this emulsion on young adult Swiss mice. Control mice received the same amount of allantoic fluid diluted with saline solution. A third control group was injected with saline solution alone.

Mice of each group were tested for antiviral resistance by intranasal instillation of graded doses of homologous influenza virus. He found that, 4 to 8 weeks after vaccination, mice that had been injected with the non-viable virus alone were resistant to about 100 MLD of homologous living virus. After 26 weeks no post-vaccination immunity could be detected. In contrast, mice vaccinated with virus plus Freund adjuvants were resistant to about 1,000,000 MLD of homologous virus 4 to 8 weeks later, and to at least 1,000 MLD at the end of 26 weeks. The Freund adjuvants apparently increased the immunologic efficiency of the formalin-killed influenza virus approximately 10,000-fold.

The same contrast was noted in the relative antibody response of ferrets injected subcutaneously with formalized influenza virus with or without Freund adjuvants. The specific antibody titers were determined by the Hirst<sup>7</sup> inhibition technique. In the control group injected with the virus alone the mean titer rose to 388 Hirst units by the end of 2 weeks. From this it gradually fell to 91 Hirst units by the end of 18 weeks. In the group injected with virus plus Freund adjuvants, the titer rose to 10,000 units by the 3rd week, gradually falling to 2,520 units by the end of 18 weeks. There was thus an apparent 27-fold increase in antibody power as a result of the Freund adjuvants.

Friedewald found that another acid-fast organism, *Mycobacterium butyricum*, could be substituted for the tubercle bacilli in the Freund emulsion with no decrease in its immunizing power. He is of the opinion, however, that it is unlikely that any adjuvants thus far tested can

be safely used in human medicine. Attempts to find safer adjuvants are now in progress.

There is as yet no generally accepted theory as to the mechanism of adjuvantic potentiation of weak vaccines.

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#### RIVER FEVER GROUP-RICKETTSIAL DISEASE (TSUTSUGAMUSHI FEVER)\*

Recently, on the Pacific Coast, much interest and discussion have centered around this rickettsial disease. Apparently, too, convalescent patients from military battle areas are being returned for further care and study. Therefore, it can be expected that "River Fever" will be investigated in all its phases, especially as to treatment and its possible control. Certain well-known characteristics and sufficient data, however, have been accumulated from which some comments may be timely.

At the very first, there may be pointed out that the classification of all rickettsial diseases, their various clinical and vector factors, and areas of distribution have undergone many changes in the past few years. The insect vectors of Tsutsugamushi Fever are the mites *Trombicula akamushi* and *deliensis*, and the animal carrier of these insects is mainly the field mouse, *Microtus montebelloi*. The heretofore recognized area distributions have been Japan, South Asia and certain Pacific islands. On the Pacific Coast there has been observed on rats, the presence of a mite, *Liponyssus bacoti*, but its relation to the spread of any of the rickettsias is not proved.

The field evidence of infections from "River Fever" concentrates on visible indications of insect bites, usually occurring near the groin, genitalia, axilla, back or extremities, and the presence of mites identified as vectors. Quite often there is left some pigmentation or necrotic bases at the bite sites. The symptoms, within ten days of the insect bite, of fever, malaise, headache, tender glands, skin eruptions and hyperesthesia, impaired hearing, parotitis, stomatitis, bronchitis, pneumonitis or pneumonia with leucopenia, enlarged liver and spleen, offer a probable clinical diagnosis. Convalescence may be quite prolonged

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